Clinical review

Pulmonary tuberculosis: diagnosis and treatment

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Tuberculosis remains a worldwide problem despite well documented, well publicised methods of prevention and cure. Poverty and HIV infection are major reasons for its persistence.[1 2] We review the diagnosis, treatment, and prevention of tuberculosis.

How is pulmonary tuberculosis diagnosed?

Symptoms and signs

Literature, opera, and art have popularised the traditional symptoms and signs of pulmonary tuberculosis (box): cough, sputum, haemoptysis, breathlessness, weight loss, anorexia, fever, malaise, wasting, and terminal cachexia figure in various combinations, not only in the descriptions of the heroes, heroines, and villains but also among the artists, poets, and musicians themselves.[3] However, none of these symptoms is peculiar to tuberculosis. Nowadays, patients with pulmonary tuberculosis who present the full spectrum of symptoms and signs are unusual in developed countries, but doctors and health workers often see such patients in developing countries. Lung cancer has become a more common cause of some or all of these symptoms in developed countries, and, as cigarette smoking increases, this may well become the case in developing countries.

Epidemiological clues to diagnosis

Among immigrants to the West from the Indian subcontinent, sub-Saharan Africa, South East Asia, the Baltic states and Russia (especially if they were previously imprisoned[4]), the prevalence of tuberculosis is much higher than among the native white population.[2 5] In the native population, tuberculosis is most commonly found among people living in poor conditions and in deprived areas, especially in elderly people and those with unstable social or psychiatric backgrounds, such as hostel dwellers, street dwellers, alcoholics, and drug misusers, as well as in immunocompromised patients.[6–8] In developing countries, tuberculosis is most common among very poor people, especially those who are severely malnourished or HIV positive.[1 8 9] Awareness, in both primary and secondary care, of these epidemiological facts increases the chances of prompt diagnosis of tuberculosis. Whereas postviral cough, asthma, reflux oesophagitis, postnasal drip, or lung cancer are more likely explanations in developed countries, cough that persists for more than three weeks despite treatment with a broad spectrum antibiotic should, in developing countries of Africa, Asia, and Europe, lead to examination of at least two specimens of sputum for tubercle bacilli, one of which should be an early morning specimen.[10] Prompt diagnosis is essential to ensure prompt treatment and thus rapid reduction in infectivity.

Symptoms and signs of tuberculosis

- Cough—usually productive
- Sputum—usually mucopurulent or purulent
- Haemoptysis—not always a feature, volume variable
- Breathlessness—gradual increase rather than sudden
- Weight loss—gradual
- Anorexia—variable
- Fever—may be associated with night sweats
- Malaise—patient may realise only retrospectively, when feeling better after treatment
- Wasting and terminal cachexia—late, ominous signs

Confirming the diagnosis

Most tuberculosis programmes use direct smear examination of sputum but, if resources permit, culture is desirable. Reliable susceptibility testing is a luxury few developing countries can afford, although it is especially desirable for purposes of re-treatment. Rapid methods of culture and susceptibility testing are widely available in the wealthier nations. Molecular techniques have provided quick, sensitive, and specific tests for *Mycobacterium tuberculosis*—such as polymerase chain reaction, DNA and RNA probes, and γ interferon tests—but these are expensive and technically demanding.[5] They are most useful in diagnosing multi-drug resistant organisms quickly and in differentiating *M tuberculosis* from other, non-infectious mycobacterial species.

What are the roles of tuberculin skin testing and chest radiography?

Tuberculin testing is helpful in ranking tuberculosis among the differential diagnoses of conditions with symptoms, signs, and radiological changes that would

Sources and selection criteria

We both have considerable experience in tuberculosis and of the research and guidelines that underpin modern management.

The review is based on this experience and on our knowledge of the literature over the past 50 years.

The references provide access to this literature, in themselves and in their own lists of references

Antituberculosis regimens for various scenarios[5 14-16]

Standard	Standard in some developing countries	Mono-resistance to rifampicin	Mono-resistance to isoniazid	Multi-drug resistance
Rifampicin, 6 months	Isoniazid, 8 months	Isoniazid, 18 months	Rifampicin, 12 months	Five drugs initially, then three drugs for 18-24 months, guided where possible by susceptibility tests
Isoniazid, 6 months	Ethambutol, 8 months	Ethambutol or pyrazinamide, or both, 18 months	Ethambutol or pyrazinamide, 12 months	
Ethambutol, 2 months	Rifampicin, 2 months			
Pyrazinamide, 2 months	Pyrazinamide, 2 months			

be compatible with pulmonary tuberculosis but where sputum is negative on direct smear or culture. A strongly positive tuberculin test in such a patient who has not previously had BCG vaccination or tuberculosis increases the probability that tuberculosis is the diagnosis. In those who have previously received BCG vaccination, γ interferon tests will differentiate between that and *M tuberculosis* as a cause of the strongly positive tuberculin test.[5]

Chest radiography is a more expensive test than examination of sputum by direct smear, but when available and reliable it is an important investigation, especially when clinical suspicion of tuberculosis exists but the sputum is negative. Fluffy upper zone shadowing, frequently bilateral and often associated with cavitation, is classic, as is miliary shadowing. New, soft shadowing among old, fibrotic changes often indicates relapse of previous disease. Paratracheal, mediastinal, and hilar lymphadenopathy are not unusual in African and Indian patients with tuberculosis. In patients infected with HIV, the radiological appearances are often less specific, just as symptoms and signs may not be classical and sputum may be negative on direct smear.

Diagnosis in children

Diagnosing tuberculosis is quite difficult in children.[11–13] Although they may cough, they rarely produce sputum and may present in a non-specific manner with failure to thrive or loss of weight, reduced energy, and, perhaps, persistent fever. Contact with a relative with tuberculosis is an important pointer. Tuberculin testing may be helpful, and, when possible, a chest radiograph should be obtained or laryngeal swabs or gastric washings taken for culture.[11–13]

Treatment of tuberculosis: the modern approach

Successful treatment is as much about building rapport with the patient as about using appropriate chemotherapy. An empathic doctor or other health worker who can build a good relationship with patients is crucial to compliance with treatment and follow-up. National tuberculosis programmes that ensure, by appropriate selection and training, that health workers treat patients with respect and understanding are likely to achieve more than those that place less emphasis on good relationships with patients.

Standard chemotherapy, as recommended by the British Thoracic Society, International Union Against Tuberculosis and Lung Disease, World Health Organization, and National Institute for Health and Clinical Excellence (NICE), consists of six months of rifampicin and isoniazid (usually given as combination tablets), initially supplemented by two months of pyrazinamide and ethambutol (table).[5 14–16] A reliable preparation containing rifampicin, isoniazid, and pyrazinamide in combination is available, as is a combination tablet of all four of these first line drugs. Fixed dose combinations of drugs in a single tablet have the great advantage of reducing the possibility of emergence of drug resistance. Pyridoxine is indicated only in malnourished patients or those with conditions predisposing to peripheral neuropathy.[14] The results of susceptibility tests are nowadays usually available before the end of the two month period of intensive treatment: providing the organisms are sensitive to rifampicin and isoniazid, the other two drugs can be discontinued at the end of the first two months and rifampicin and isoniazid continued for a further four months. Whenever possible, cure should be confirmed by smear and culture of sputum at the end of treatment. If the pleural cavities are involved, the chemotherapy regimen is the same, but pleural aspiration may be needed to reduce breathlessness. If the effusion recurs, glucocorticoids for three to six weeks help to prevent or reduce further reaccumulation.[14]

How to manage drug resistance

The six month regimen has been shown to be effective only when the combination of rifampicin and isoniazid is used. If mono-resistance to rifampicin is present, then the British Thoracic Society guidelines recommend that isoniazid and ethambutol or pyrazinamide should be continued for a total of 18 months. For mono-resistance to isoniazid, these guidelines recommend continuing rifampicin and ethambutol (or

Tips for non-specialists

- A high index of suspicion is needed in immigrants, elderly people, immunocompromised patients, and people in poor living conditions
- In developing countries, check sputum for acid-fast bacilli if cough persists longer than three weeks despite broad spectrum antibiotics
- Appearances on chest radiographs are often less specific in immunocompromised patients
- In the absence of evidence of previous infection or BCG vaccination, a strongly positive tuberculin test increases the probability that tuberculosis is the diagnosis, even if sputum is negative
- Standard treatment consists of six months of rifampicin and isoniazid, with an initial two months of pyrazinamide and ethambutol; combination preparations are available
- If drug resistance is found, the regimen must be altered and treatment extended
- Cross infection is more likely if the patient is sputum positive for acid-fast bacilli on a direct smear
- Prompt contact tracing is needed for close contacts—that is, people sharing living accommodation, especially children; casual contacts are at low risk
- Treating patients at home is no more likely to lead to cross infection than treating them in hospital
- BCG vaccination should be offered to all people at high risk of encountering tuberculosis

Current and future directions for research

- Development and testing of new vaccines
- Development and testing of new drugs, ideally with shorter durations of treatment
- Research into effectiveness of programmes and means of collaboration with HIV/AIDS programmes
- Development of cheap, easily applied diagnostic methods
- Examining ways of improving concordance with treatment among doctors and patients
- Further exploration of private-public sector partnerships in managing tuberculosis

pyrazinamide) for 12 months. The same provisos apply in situations in which drug intolerance precludes the use of rifampicin or isoniazid.[14] A single drug should never be added to a failing regimen, as this may lead to resistance arising to that drug as well. If resistance to both rifampicin and isoniazid is present, the patient must be managed primarily by a chest physician with expertise in treating multi-drug resistant tuberculosis.[5 14 17] By necessity, the regimen will include second line drugs that often have unwanted effects. Even with an expert chest physician, backed by a reliable tuberculosis laboratory, management remains challenging and mortality is high.

What if the budget is inadequate for rifampicin?

Lately the Global Drug Facility, through the Stop TB Partnership, has enabled many countries to provide the standard six month regimen used in the developed world. In other countries that cannot afford rifampicin for six months, the recommended regimen consists of rifampicin, isoniazid, pyrazinamide, and ethambutol or streptomycin for the first two months, followed by six further months of isoniazid and ethambutol or, if ethambutol is not available and the prevalence of HIV/AIDS is low, isoniazid and thiacetazone.[12 15 16] After the initial intensive phase, some countries may be able to choose a continuation phase of thrice or twice weekly high dose isoniazid and rifampicin for four months, regimens of proved efficacy when the taking of each dose is supervised.

Supervised chemotherapy is one of the five cornerstones of the DOTS (directly observed therapy, short course) policy; the other four components are government commitment to the national tuberculosis programme, a reliable tuberculosis microscopy and laboratory service, good recording and reporting, and regular, uninterrupted drug supplies. Motivated health workers, managed and supervised competently and fairly, are important, whether or not the programme uses full DOTS, partial DOTS, family/community DOTS, or unsupervised chemotherapy.[16] Despite initial insistence by WHO that health workers supervise every dose, a Cochrane review of clinical trials has not been able to show that such supervision ensures better results than those obtained by other ways of giving chemotherapy.[18]

Treatment of pulmonary tuberculosis in patients with HIV/AIDS is complicated by interactions between antiretroviral and antituberculosis drugs, particularly rifampicin. The standard regimens for the two conditions are usually modified to minimise unwanted effects.[14 16 19 20]

Control and prevention of tuberculosis: public health measures

Good nutrition and housing contributed to the decline of tuberculosis in western Europe before effective antituberculosis drugs were available, but prompt diagnosis and treatment remain the most effective means of controlling tuberculosis.

What is the current role of BCG vaccination?

BCG vaccination in infants provides a certain degree of protection against serious forms of tuberculosis, especially tuberculous meningitis and disseminated tuberculosis.[13 21] In the United Kingdom, at a time when tuberculosis was more common, BCG vaccination of adolescents was 70-80% effective in reducing the incidence of all forms of tuberculosis later in life.[17] In the UK today, the annual increase in tuberculosis stems mainly from London (especially boroughs with large populations of immigrants) and the larger conurbations of the Midlands, north west England, and north east England. The national programme of BCG vaccination for schoolchildren has been discontinued and replaced by a policy of selective vaccination of neonates and older people at high risk of infection, such as schoolchildren in areas where prevalence is ≥40 per 100 000, health workers, prison staff, hospital workers, and immigrants from countries with high prevalence.[5] In high prevalence countries, WHO and the International Union Against Tuberculosis and Lung Disease still recommend universal neonatal BCG vaccination,[12 15 16] pending development of a more effective vaccine.

How to deal with the problem of cross infection

Cross infection is much more likely to occur from patients whose sputum is positive on direct smear than from those with negative smears. The people most likely to be infected are close contacts (family and others who share living accommodation, especially children, or those who work closely and regularly with

Additional educational resources

Further reading

Seaton A, Seaton D, Leitch AG, eds. *Crofton and Douglas's respiratory diseases*. 5th ed. Oxford: Blackwells, 2000

Gibson GJ, Geddes DM, Costabel U, Sterk PJ, Corrin B. *Respiratory medicine*. 3rd ed. London: Elsevier Science, 2003

Davies PDO, ed. *Clinical tuberculosis*. 3rd ed. Oxford: Oxford University Press, 2003

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Various papers on tuberculosis: *Lancet* 2006;367:877, 878, 903, 926, 938-57

Information resources for patients

International Union Against Tuberculosis and Lung Diseases, 68 Boulevard Saint Michel, 75006 Paris (www.iuatld.org)

Stop TB Partnership, World Health Organization, Geneva, Switzerland (www.stoptb.org)

TB Alert, 22 Tiverton Road, London NW10 3HL (www.tbalert.org)

British Lung Foundation, 73-75 Goswell Road, London EC1V 7ER (www.lunguk.org)

Summary points

- In Western countries, tuberculosis is most common among immigrants and poor or malnourished people
- The diagnosis should be confirmed by sputum examination for *Mycobacterium tuberculosis* and, if available, chest radiography
- Tuberculosis should be treated promptly with the recommended four drug regimen, reducing to two drugs after two months and continuing for four further months
- Admission to hospital is necessary only if the patient is too ill to be managed at home or cannot tolerate the treatment
- After two weeks' treatment, smear positive patients can be considered non-infectious; smear negative patients are rarely infectious anyway
- BCG vaccination can be used selectively in a population, but in areas with high prevalence it should be given to all neonates
- An adequately resourced, well organised tuberculosis programme should be a priority in developing and developed countries

the patient or socialise regularly in an enclosed area). Prompt tracing of the close contacts of patients with sputum smear positive pulmonary tuberculosis is important in finding and treating the source of the original infection and people infected by the patient. Procedures will depend on BCG status and may include tuberculin testing, chest radiography, or both as outlined by the British Thoracic Society and the NICE guidelines.[5 17] People with disease should be fully treated. Some of those with infection, but no evidence of disease, will need prophylaxis with isoniazid for six months or rifampicin and isoniazid for three months.[5 17] Casual contacts are at low risk and should be traced only if 10% or more of the close contacts develop disease.[17] If resources are available, developing countries too should have protocols for identifying, tracing, and examining close contacts of patients with pulmonary tuberculosis, especially of smear positive patients.

Cross infection usually occurs among household contacts before treatment is started: the Madras study showed that treating patients at home was not associated with more cross infection than admitting them to hospital for treatment.[22] Chemotherapy should be started as soon as possible after diagnosis. Referral to secondary care can follow later, if such referral is national practice. Within two weeks of starting chemotherapy the patient becomes non-infectious, even though bacilli may still be seen on direct smear.[23] Therefore, if patients need to be admitted to hospital, and circumstances permit, they should be segregated from other patients on the ward until 10-14 days of chemotherapy have been given.[5 17] Barrier nursing is not necessary, except for patients with multi-drug resistant tuberculosis, who should be managed in a negative pressure room vented to the outside.[5 17] In countries without such facilities, as much segregation as is feasible should be the aim, and the patient should be discharged home as soon as possible. Better still, admission should be avoided unless clinically imperative.

If they are to be effective, control and prevention programmes need adequate funding, just as treatment programmes need proper resources of manpower, drugs, and recording and reporting systems. The Stop TB Partnership's second global plan to stop tuberculosis identifies the strategy and resources necessary to reduce tuberculosis.[24] It is now up to governments in developing countries to commit sufficient resources to tuberculosis control and to donor agencies and countries to follow the generous example set by the Bill and Melinda Gates Foundation.

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